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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

Election/Restriction

1. Applicant has elected Group I without traverse. Non-elected claims (63-69) of Group II have been canceled without prejudice towards further prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 1-30 are rejected under 35 U.S.C. 102 (a) as anticipated by Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174).

Beutler et al teaches a method for detecting polymorphisms in the uridine diphosphate glucuronosyltransferase (UGT1A1) gene promoter (Abstract) comprising determining the number of thymidine-adenine (TA) repeats in the promoter (MATERIALS AND METHODS SECTION and Figure 1), wherein the number of TA repeats correlates with the expression of the

gene (Abstract, Page 8170, column 1, line 29 to column 2, line 18, and DISCUSSION Section, first four paragraphs).

Beutler et al teaches a method comprising the steps of:

a) obtaining DNA from an individual (MATERIALS AND METHODS SECTION , lines 1-9).

b) amplifying all or part of the UGT gene promoter contained in the DNA by PCR (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 3-12).

c) determining the number of TA repeats in the promoter by sequencing gel electrophoresis of the amplified DNA (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 12-25 and Figure 1).

Beutler et al teaches a method wherein the polymorphism comprises an allele, the allele selected from the group consisting of five TA repeats, [TA]5, six TA repeats, [TA]6, seven TA repeats, [TA]7, and eight TA repeats, [TA]8 (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 22-25 and Figure 1).

Beutler et al teaches a method wherein the promoter has a genotype selected from the group consisting of [TA]6/[TA]8, [TA]7/[TA]8, and [TA]8/[TA]8.

5. A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-23 are rejected under 35 U.S.C. 102 (b) as anticipated by Bosma et al. (New England J. Medicine (1995), Vol. 333, p. 1171-5) ~~(Hepatology, (1992), Vol. 15, pages 941-947)~~.

Bosma et al teaches a method for detecting polymorphisms in the uridine diphosphate glucuronosyltransferase (UGT1A1) gene promoter (Abstract) comprising determining the number of thymidine-adenine (TA) repeats in the promoter (METHODS SECTION and Figure 1), wherein the number of TA repeats correlates with the expression of the gene (Abstract and Figure 3).

Bosma et al teaches a method comprising the steps of:

a) obtaining DNA from an individual (METHODS SECTION , lines 1-35).

b) amplifying all or part of the UGT gene promoter contained in the DNA by PCR (METHODS SECTION , Nucleotide sequencing of coding and upstream regions of the gene for bilirubin UDP-Glucuronosyltransferase 1 subsection).

c) determining the number of TA repeats in the promoter by sequencing gel electrophoresis of the amplified DNA (METHODS SECTION , Functional evaluation of the variant TATAA element subsection and Figure 1).

Bosma et al teaches a method wherein the polymorphism comprises an allele, the allele selected from the group consisting of five TA repeats, [TA]5, six TA repeats, [TA]6, seven TA repeats, [TA]7, and eight TA repeats, [TA]8 (Figure 1, Figure 2, Figure 3 and Table 1).

Bosma et al teaches a method wherein the promoter has a genotype selected from the group consisting of [TA]6/[TA]8, [TA]7/[TA]8, and [TA]8/[TA]8 (Table 1 and Figure 3).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-62 are rejected under 35 U.S.C. 103 (a) over either Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174) or in the alternative Bosma et al. (Hepatology, (1992), Vol. 15, pages 941-947), either in view of Clarke et al. (Handbook of Experimental Pharmacology, (1994), Vol. 112, pages 3-43).

Beutler et al and Bosma et al teach the method of claims 1-30 and 1-23 respectively as described above.

Beutler et al or Bosma et al do not teach the a method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics and a method for optimizing drug dosage and a method for predicting an individual's sensitivity to xenobiotics.

Clarke et al teach the method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics by UDPGT and a method for optimizing drug dosage and a method for predicting an individual's sensitivity to xenobiotics (SECTION E, page 24 to page 28, Tables 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the classical glucuronidation of drugs and xenobiotics by UDPGT model of Clarke et al. in the method of Beutler or Bosma et al., since Clarke et al. states "Such method should prove to be of great benefit to the pharmaceutical industry as drugs which have cytotoxic glucuronides or are metabolized too rapidly to be of therapeutic value can be identified, chemically modified and improved (Page 28, last 4 lines)." Clarke et al expressly connects Gilbert syndrome and dosage effects of Acetaminophen to UGT gene, while both Bosma et al and Beutler et alconnect UGT mutation to Gilbert syndrome and to ~~primer~~ promoter activity, thereby connecting the Acetaminophen dosage and metabolism to the activity of the UGT gene promoter. An ordinary practitioner would have been motivated to combine and compare the classical glucuronidation of drugs and xenobiotics by UDPGT model of Clarke et al. in the method of Beutler or Bosma et al in order to achieve the express advantages noted by Clarke et al. of the glucuronidation techniques which can provide method of great benefit to the pharmaceutical industry as drugs which have cytotoxic glucuronides or are metabolized too rapidly to be of therapeutic value can be identified, chemically modified and improved.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703)

306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Kr. Chakrabarti

Arun Chakrabarti,

Patent Examiner,

May 2, 2000

JEFFREY FREDMAN
PRIMARY EXAMINER